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Systematic review

Novel point-of-care biomarker combination tests to differentiate acute bacterial from viral respiratory tract infections to guide antibiotic prescribing: a systematic review

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ABSTRACT

Background: Acute respiratory tract infections (RTIs) are the most common reason to seek medical care, with many patients receiving inappropriate antibiotics. Novel testing approaches to identify aetiology at the point-of-care are required to accurately guide antibiotic treatment.
Objective: To assess the diagnostic accuracy of biomarker combinations to rapidly differentiate between acute bacterial or viral RTI aetiology.
Data sources: MEDLINE, Embase and Web of Science databases were searched to February 2021.
Study eligibility criteria: Diagnostic accuracy studies comparing accuracy of point-of-care and rapid diagnostic tests in primary or secondary care, consisting of biomarker combinations, to identify bacterial or viral aetiology of RTI.
Methods: Risk of bias was assessed using the QUADAS-2 tool. Sensitivity and specificity of tests reported by more than one study were meta-analysed using a random effects model.
Results: Twenty observational studies (3514 patients) were identified. Eighteen were judged at high risk of bias. For bacterial aetiologies, sensitivity ranged from 61% to 100% and specificity from 18% to 96%. For viral aetiologies, sensitivity ranged from 59% to 97% and specificity from 74% to 100%. Studies evaluating two commercial tests were meta-analysed. For ImmunoXpert, the summary sensitivity and specificity were 85% (95% CI 75%–91%, $k = 4$) and 86% (95% CI 73%–93%, $k = 4$) for bacterial infections, and 90% (95% CI 79%–96%, $k = 3$) and 92% (95% CI 83%–96%, $k = 3$) for viral infections, respectively. FebriDx had pooled sensitivity and specificity of 84% (95% CI 75%–90%, $k = 4$) and 93% (95% CI 90%–95%, $k = 4$) for bacterial infections, and 87% (95% CI 72%–95%; $k = 4$) and 82% (95% CI 66%–86%, $k = 4$) for viral infections, respectively.
Conclusion: Combinations of biomarkers show potential clinical utility in discriminating the aetiology of RTIs. However, the limitations in the evidence base, due to a high proportion of studies with high risk of bias, preclude firm conclusions. Future research should be in primary care and evaluate patient outcomes and cost-effectiveness with experimental study designs.
Clinical trial: PROSPERO registration number: CRD42020178973. **Henry C. Carlton, Clin Microbiol Infect 2021;■:1**

Introduction

Antimicrobial resistance is a major worldwide health issue and is driven, in part, by inappropriate antibiotic use [1–4]. In Europe,

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acute respiratory tract infections (RTIs) are the most common reason for antibiotic prescription [5,6]. Previous studies suggest that 38%–66% of antibiotics prescribed for RTIs are inappropriate and in English primary care, more than 60% of all inappropriate antibiotic prescriptions are related to RTIs or conditions of the ears, nose and throat [7–9]. Although the causes of inappropriate prescription are multifactorial, a key aspect is diagnostic uncertainty [10–14]. Current testing approaches to guide prescription do not provide the prompt diagnostic accuracy needed to sufficiently balance patient health with antibiotic stewardship [15,16].

Many approaches to identify an infectious aetiology are not applicable to a point-of-care setting. Traditional culture-based approaches and mass spectrometry are not portable to the bed-side, have varied diagnostic accuracy and are restricted to cultivatable bacteria [17,18]. Although PCR tests are being developed with decreased turnaround times (e.g. for coronavirus disease 2019) [19], important drawbacks of these tests include low pathogen detection rates of 20% in adults with respiratory symptoms and in some settings, colonization of non-pathogenic respiratory tract biota occurs in over 50% of instances [20–24]. Difficulty in differentiating non-pathogenic microbes is evident in all pathogen-focused approaches and is complicated by diverse commensal bacteria and disputed pathogenic roles of viruses [25–28]. Rapid antigen detection testing is better suited to a point-of-care setting, but variable and sub-optimal sensitivity restricts their use for routine diagnostics [29–31]. Ultimately, no viable testing approach exists to accurately or reliably discriminate RTI aetiology at the point-of-care.

Delayed diagnosis and treatment of bacterial infections can directly affect patient outcomes. Withholding antibiotics because of missed or delayed diagnosis may occur in 24%–40% of bacterial infections in secondary care [15,32–34], and is associated with poorer clinical outcomes, longer hospitalization and increased disease incidence [35–39]. The overuse of antibiotics has its own implications, with antibacterial resistance threatening key medical procedures. In the USA, almost half of post-surgical and nearly one-quarter of post-chemotherapy infections were caused by bacteria resistant to standard prophylactic antibiotics and a further 10% drop in antibiotic efficacy could potentially result in an additional 2000 deaths a year [40]. Consequently, early discrimination of acute RTI aetiology has both short-term and long-term benefits for patient outcomes, and novel point-of-care diagnostic approaches are necessitated.

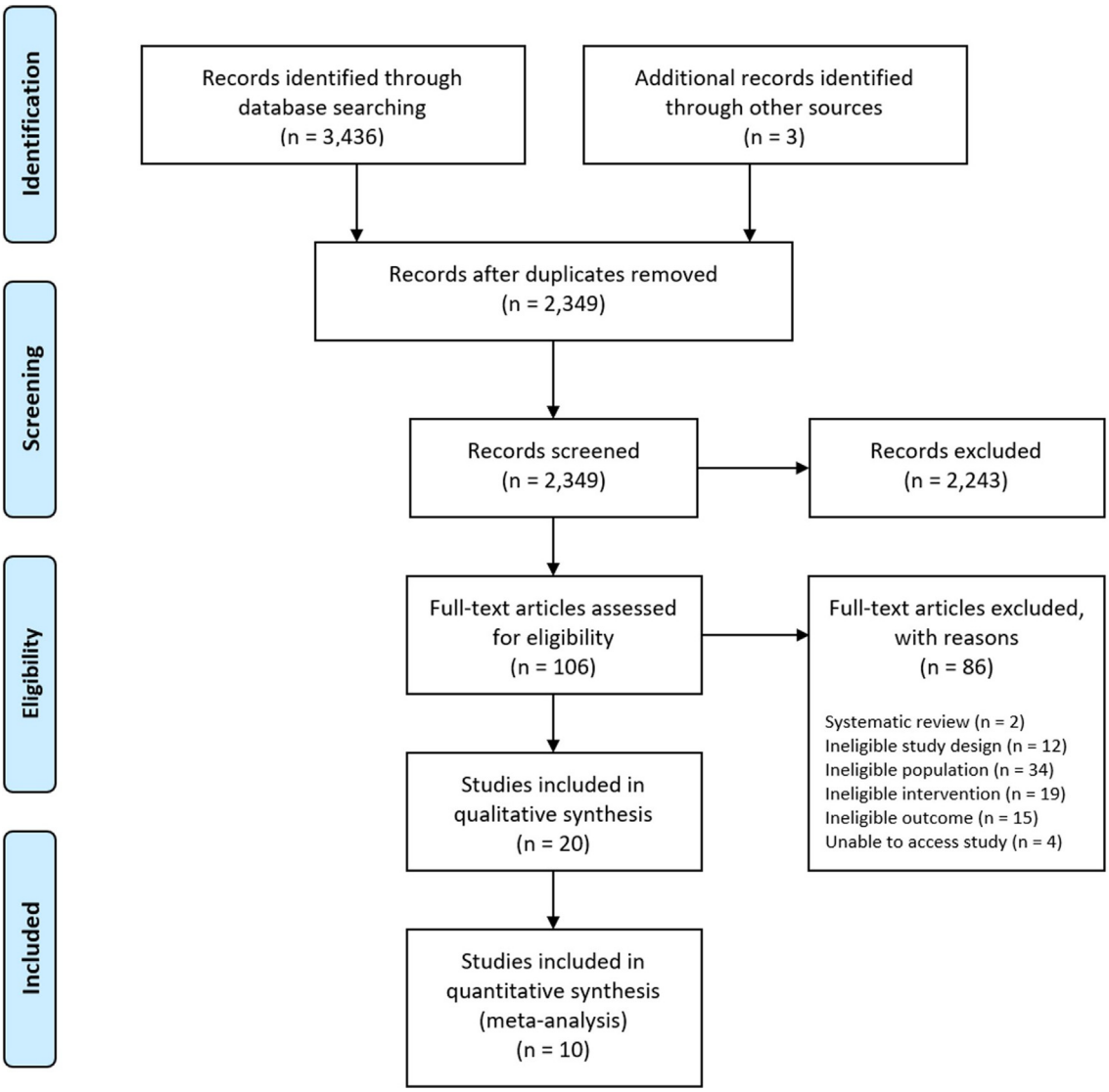

Fig. 1. PRISMA study flow diagram.

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Table 1
Main characteristics of included studies

Test	Biomarkers[a]	Age group[b]	Number of participants		Test accuracy comparison(s)	Target condition	Reference standard	Study design	Reference
ImmunoXpert	TRAIL, IP-10, and CRP	Adults	218	Bacterial $n = 43$ Viral $n = 109$ Other $n = 66$	Bacterial from non-bacterial and viral from non-viral	LRTI	Expert panel	Cohort	Shani 2019 [78]
		Paediatrics	657	Viral $n = 465$ Not-viral $n = 192$	Viral from non-viral	RTI	Expert panel	Cohort	Mencaroni 2019 [71]
		Adults and paediatrics	216	Bacterial/bacterial-viral $n = 112$ Viral $n = 104$	Bacterial/bacterial−viral from viral	RTI	Expert panel	Nested case−control	Ashkenazi-Hoffnung 2018 [81]
		Adults and paediatrics	161	Bacterial/bacterial-viral $n = 88$ Viral $n = 36$ Other $n = 37$	Bacterial/bacterial-viral from viral	LRTI	Expert panel	Cohort	Stein 2018 [84]
		NR	114	Bacterial $n = 63$ Viral $n = 51$	Bacterial versus viral	Pneumonia (unspecified)	Expert panel	Nested case−control	Mastboim 2019 [86]
		NR	302	Bacterial $n = 61$ Viral $n = 241$	Bacterial versus viral	URTI	Expert panel	Nested case−control	Oved 2017 [87])
FebriDX	CRP and MxA	Adults	47	Bacterial $n = 8$ Viral $n = 35$ Non-infectious $n = 4$	Bacterial from viral and non-infectious and viral from bacterial and non-infectious	RTI	Clinical algorithm	Cohort	Karim 2020 [80]
		Adults	54	Bacterial/bacterial-viral $n = 20$ Viral $n = 10$ Healthy $n = 24$	Bacterial/bacterial−viral from viral/healthy	RTI	Clinical algorithm	Case−control	Sambursky 2015 [77]
		Adults and paediatrics	205	Bacterial $n = 25$ Viral $n = 53$ Not bacterial or viral $n = 127$	Bacterial from viral/healthy and viral from bacterial/healthy	URTI	Clinical algorithm with clinician override	Cohort	Self 2017 [82]
		Adults and paediatrics	220	Bacterial/bacterial−viral $n = 34$ Viral $n = 124$ Other $n = 62$	Bacterial from non-bacterial and viral from non-viral	URTI	Clinical algorithm with clinician override	Cohort	Shapiro 2018 [83]
		NR	111	Viral $n = 69$ Not-viral $n = 42$	Viral from non-viral	RTI	Diagnostic microbiological investigation	Cohort	Beard 2019 [85]
Other tests	IL-5, IL-6, and IFN-γ or CRP, IL-6, and IL-27	Adults	104	Pneumococcal $n = 48$ Bacterial−viral $n = 39$ Viral $n = 17$	Pneumococcal/bacterial−viral from viral	CAP	Clinical algorithm	Nested case−control	Burgmeijer 2019 [75]
	CRP and PCT	Adults	25	Bacterial/bacterial−H1N1 $n = 16$ H1N1 $n = 9$	Bacterial/bacterial−H1N1 from H1N1	CAP	Diagnostic microbiological investigation	Cohort	Ingram 2010 [79]
	CRP and neopterin	Adults	198	Bacterial $n = 105$ Bacterial−viral $n = 12$ Viral $n = 81$	Bacterial/bacterial−viral from viral	RTI	Clinical algorithm	Nested case−control	Rainer 2009 [76]
	CRP and MPV or neutrophil and lymphocyte counts	Paediatrics	52	Bacterial $n = 31$ Viral $n = 21$	Bacterial versus viral	Pneumonia (unspecified)	Clinical algorithm	Nested case−control	Bekdas 2014 [68]
	IL-27, PCT and WBC	Paediatrics	188	Bacterial $n = 52$ Viral $n = 136$	Bacterial versus viral	RTI	Radiographic diagnosis	Nested case−control	Eckerle 2016 [69]
	Haptoglobin, fractalkine, resistin, GCSF and NGAL	Paediatrics	86	Bacterial/bacterial-malarial/ bacterial-viral $n = 19$ Viral/viral-malarial $n = 32$ Malarial $n = 1$ Healthy control $n = 16$	Bacterial from viral/malarial	Pneumonia (unspecified)	Clinical algorithm	Nested case−control	Gillette 2021 [74]
	CRP, PCT, WBC and ESR	Paediatrics	55	Pneumococcal $n = 25$ Pneumococcal-viral $n = 13$ Viral $n = 17$	Pneumococcal/pneumococcal-viral from viral	CAP	Diagnostic microbiological investigation	Nested case−control	Korppi 2004 [70]
	Haptoglobin, IL-10 and TIMP-1 or SVMM-selected biomarkers or MLRM-selected biomarkers	Paediatrics	80	Bacterial $n = 23$ Viral $n = 30$ Malarial $n = 27$	Bacterial from viral/malarial and viral from bacterial/ malarial	Pneumonia (unspecified)	Clinical algorithm	Nested case−control	Valim 2016 [72]

(*continued on next page*)

Table 1 (*continued*)

Test	Biomarkers[a]	Age group[b]	Number of participants	Test accuracy comparison(s)	Target condition	Reference standard	Study design	Reference
	IL-6 and IL-10	Paediatrics	349 MP $n = 182$ RSV $n = 167$	MP versus RSV	Pneumonia (unspecified)	Diagnostic microbiological investigation	Nested case–control	Zhou 2017 [73]

Abbreviations: CAP, community-acquired pneumonia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCSF, granulocyte colony-stimulating factor; H1N1, influenza A virus subtype H1N1; IFN-γ, interferon-γ; IL-5, interleukin-5; IP-10, interferon-γ-induced protein 10; LRTI, lower RTI; MP, *Mycoplasma pneumoniae*; MPV, mean platelet volume; MxA, myxovirus resistance protein-1; NGAL, neutrophil gelatinase-associated lipocalin; NR, not reported; PCT, procalcitonin; RSV, respiratory syncytial virus; RTI, respiratory tract infection; TIMP-1, tissue inhibitor of metalloproteinase-1; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; URTI, upper RTI; WBC, white blood cell count.

[a] Biomarkers: SVMM (support vector machine model) biomarkers = CRP, creatinine kinase myocardial band, haptoglobin, IL-10 and matrix metalloproteinase-9; MLRM (multinomial logistic regression model) biomarkers for bacterial aetiology = α-1 antitrypsin, creatinine kinase myocardial band, GCSF, haptoglobin, immunoglobulin M, leptin, matrix metalloproteinase-3, matrix metalloproteinase-9 and phenylalanine ammonia-lyase-1; MLRM biomarkers for viral aetiology = α-1 antitrypsin, α2-macroglobulin, CRP, IL-18, matrix metalloproteinase-9 and thyroxine-binding globulin.

[b] Paediatric <18 years; adults ≥18 years.

The application of proteomic methodology to RTI diagnostics is a significant development. Bacterial and viral aetiologies in RTIs have measurable differences in host-response, allowing these biomarkers to be surrogate markers of infection aetiology [41,42]. C-reactive protein (CRP) and procalcitonin (PCT) increase more extensively in bacterial than in non-bacterial RTIs and, when used to guide treatment, meta-analyses of experimental research have shown significant reductions in antibiotic prescription compared with normal practice [43–46]. However, lone biomarkers have limitations as CRP has insufficient diagnostic accuracy, disputed correlation with bacterial load and can produce drastic increases in response to some viruses while the diagnostic accuracy of PCT has been shown to vary significantly [41,47–51]. Recent approaches have attempted to increase diagnostic accuracy through combining multiple biomarkers.

This study aims to assess the validity of testing multiple biomarkers, at the point-of-care, to identify bacterial or viral aetiology in patients with acute RTI.

Materials and methods

We followed recommended methods for systematic review [52,53] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagnostic Test Accuracy criteria 2018 (see Supplementary material, Table S1) [54]. A protocol was pre-registered [55].

Eligibility criteria

Our review included diagnostic accuracy studies, reporting on point-of-care and rapid diagnostic tests consisting of more-than-one biomarker to identify bacterial or viral aetiology, in the general population presenting to primary or secondary care with acute RTI symptoms. Tests could be compared to any reference standard.

Literature search

We searched without language or date restriction in the MEDLINE, Embase and Web of Science databases up until February 2021. The search strategy combined terms for 'respiratory tract infections', 'point-of-care tests/rapid test or combination tests' and 'biomarkers' with a diagnostic test accuracy and systematic review study design filter (see Supplementary material, Table S2) [56,57]. To help validate these filters, a MEDLINE search was piloted with and without the filters, with the difference set screened. As no relevant articles were identified, we were satisfied that addition of the filter would not compromise sensitivity. Additional records were identified by screening relevant systematic reviews identified by the search.

Study selection

Study selection at both abstract and full-text stage was carried out independently by two investigators (HC and ME). Abstract screening was conducted using Rayyan [58] and full-paper screening decisions were recorded in a custom-made Microsoft Access database. Discrepancies were resolved through discussion or referral to third reviewer (JS). We contacted study authors to request further information if articles appeared relevant but did not fulfil an inclusion criterion.

Data extraction

Data were extracted from each eligible study using a piloted, pre-defined form built into a custom-made Microsoft Access

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database by one author (HC) and checked by another (ME), with discrepancies resolved through discussion or referral to a third reviewer (JS). Data extraction consisted of: study characteristics, patient characteristics, reference standard details, index test details and accuracy outcomes.

Risk of bias assessment

The Quality Assessment of Diagnostic Accuracy Studies tool-2 (QUADAS-2) was used to assess methodological quality [59]. QUADAS-2 consists of four key domains: patient selection, index test, reference standard, and flow and timing. Risk of bias was assessed in all four domains while concerns over applicability were assessed in the first three. Domains were judged as low, unclear or high based on the answers to the signalling questions and judgements were checked by another author and our clinical advisor (PM). Graphical representation was produced through Revman (version 5.4).

Data handling and analysis

Index tests were classified based on the aetiology, bacterial or viral, that they aimed to identify. Negative results included indeterminate, other infection aetiology or non-infectious cause. All tests identifying the same aetiology were compared with forest plots of sensitivity and specificity, using the 'meta' package for R (version 3.6.3) [60,61] Positive predictive values and negative predictive values were illustrated in a hypothetical population of 1000 acute RTI patients presenting to primary and secondary care with defined infection aetiology prevalence [62,63]. Receiver operating characteristics plots were produced, grouping all index tests identifying the same aetiology, using MetaDTA [64]. Meta-analysis was restricted to index tests reported by more-than-one study. We presented the data graphically in forest plots with summary estimates for sensitivity and specificity, based on the random effects bivariate binomial model of Chu & Cole with no covariates, using MetaDTA [64,65].

Results

Study inclusion

Our electronic searches identified 3436 records (Fig. 1). Of the 2349 unique records, 2243 records were excluded based on abstract screening and 106 underwent full-text review. Of these, 86 were excluded (see Fig. 1 for exclusion reasons) and 20 fulfilled the inclusion criteria, including a total of 3424 patients. Two systematic reviews were reviewed for relevant citations with three potentially relevant studies found that had already been identified by our electronic search [66,67]. Ten studies, reporting on two different tests, were eligible for meta-analysis.

Study characteristics

All identified studies were set in a secondary care environment (Table 1, see Supplementary material, Table S3). Included age groups were children only [68–74], adults only [75–80], mixed] or not reported [85–87]. Three studies focused specifically on upper RTIs [82,83,87], two on lower RTIs [78,84] and seven studies included patients with both upper and lower RTIs [69,71,76,77,80,81,85]. The remaining eight studies included patients with pneumonia—community-acquired [70,75,79] or unspecified [68,72–74,86]. Sample sizes ranged from 25 to 657. There were six studies with reference standards classified as expert panel, defined as aetiology decided by more than one clinician's judgement of patient presentation (see Supplementary material, Table S4) [71,78,81,84,86,87]. Eight studies had reference standards classified as clinical algorithm, where determination was based upon an algorithm of clinical signs, symptoms or investigations with [82,83] or without [68,72,74–77,80] clinician override. Diagnostic microbiological investigation as a reference standard was defined as determination through a targeted- or multiplex-approach microbiological investigation and was used in four studies [70,73,79,85]. Only one study used a reference standard of radiological investigation, which was defined as determination based on radiological findings [69].

Six studies investigated the accuracy of ImmunoXpert [71,78,81,84,86,87], which combines CRP, interferon-γ-induced protein 10 and tumour necrosis factor-related apoptosis-inducing ligand, returning results in 100 minutes. Three used a cohort design [71,78,84], which made it possible to determine the accuracy of the test in distinguishing bacterial from non-bacterial infections and viral from non-viral infections among a cohort of patients with similar symptoms. Three were nested case–control studies [81,86,87], a study design that creates a sub-cohort of patients with an exposure of interest from a fully enumerated cohort. In these three, index tests were assessed at differentiating bacterial infection cases from viral infection controls and vice versa. One of these studies [81] classified mixed bacterial-viral infections as bacterial, so we were only able to evaluate the diagnostic accuracy for bacterial aetiology, and a second [87] excluded participants with indeterminate index test results, artificially inflating the diagnostic accuracy.

Five studies investigated the accuracy of FebriDx [77,80,82,83,85], which consists of CRP and myxovirus resistance protein-1 and returns results in 10 minutes. Four used a cohort design [80,82,83,85], with one study only reporting accuracy for viral aetiological testing [85]. The fifth study used a case–control design

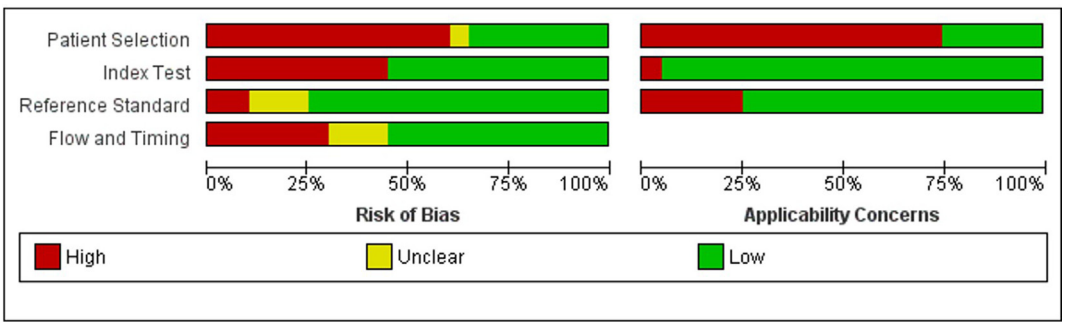

Fig. 2. Proportions of risk of bias and applicability concerns judgment by domain.

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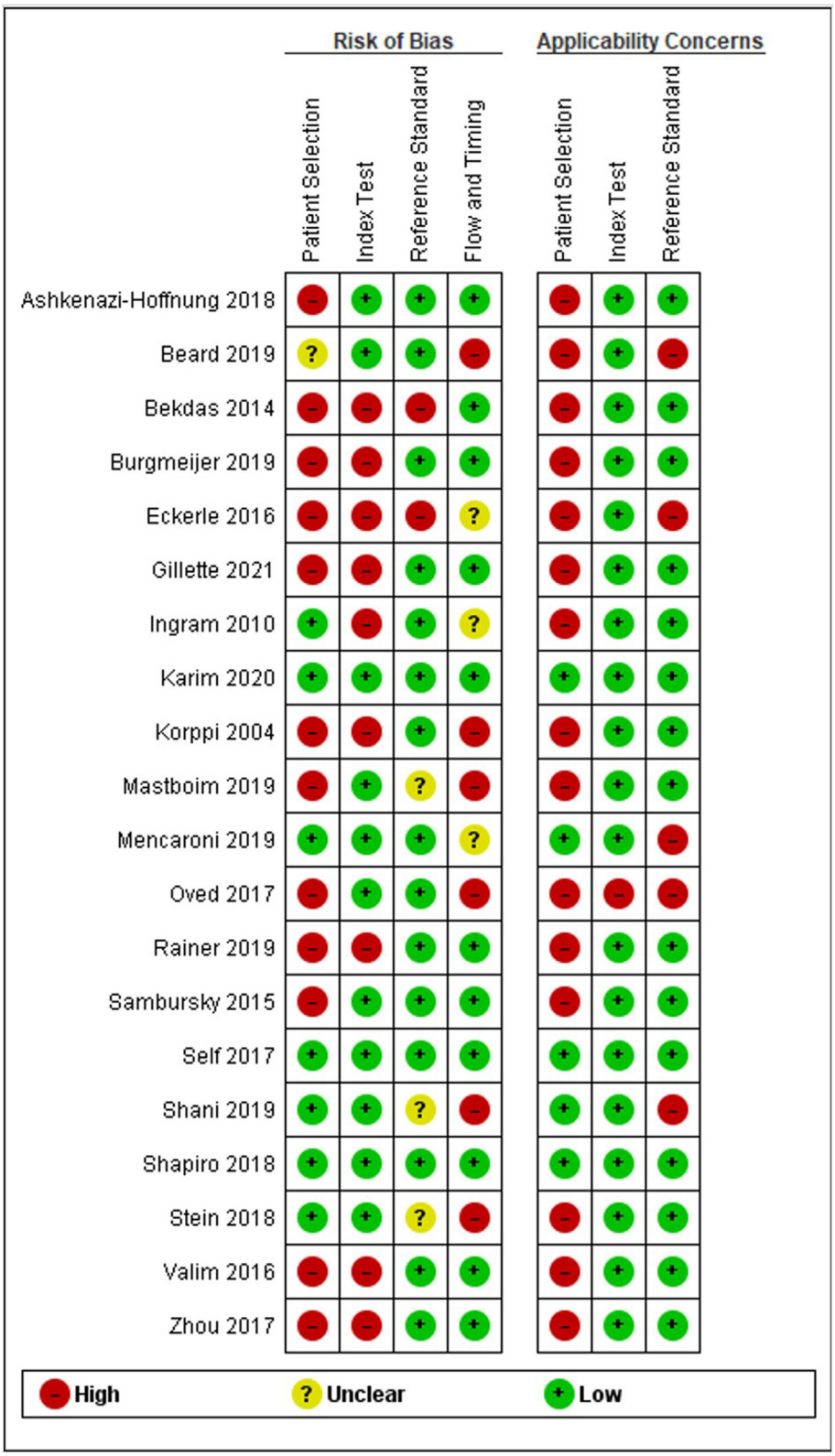

Fig. 3. Summary of risk of bias and applicability concerns judgment by study.

with an additional group of healthy participants [77], this allowed analysis of the index test to distinguish bacterial from viral and healthy participants as well as viral from bacterial and healthy participants.

The remaining nine studies each reported unique combinations of biomarkers (Table 1), all using a nested case–control design [68–70,72–76], bar one with a cohort design [79]. Two studies [68,69] had populations that allowed for comparison between

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groups of patients with bacterial and viral classification while a third was limited to bacterial accuracy data as mixed bacterial infections were classified as bacterial [76]. Four studies identified pathogen-specific infections, allowing comparisons of: pneumococcal and mixed bacterial-viral against viral [75], pneumococcal and mixed pneumococcal-viral against viral [70], bacterial and mixed bacterial–influenza A virus subtype H1N1 against influenza A virus subtype H1N1 [79], and *Mycoplasma pneumonia* [73] against respiratory syncytial virus. The remaining studies incorporated a malarial group to distinguish bacterial and viral aetiology from [72,74], with one also adding a healthy control group [74].

Quality of included studies

Risk of bias was judged per test but reported per study as no differences in risk of bias were found within tests of a study (Figs. 2 and 3, see Supplementary material, Table S5). All but three of the included studies displayed at least one domain with unclear or high risk of bias [80,82,83]. Patient selection bias was the most common reason for the high-risk judgement, in 12 studies with non-cohort designs [68–70,72–76,81,86,87]. In the index test domain, nine studies reported high risk of bias where thresholds were not pre-specified [68–70,72–76,79]. Regarding the reference standard domain, two studies [68,69] were considered at high risk of misclassification bias while three were considered at unclear risk of incorporation bias with poorly defined 'laboratory' parameters [78,84,86]. Within the flow and timing domain, five were judged to be at high risk of bias [70,78,84–87] because of inappropriate participant exclusions and one because children and adults received different reference standards [84]. Fifteen studies were judged high concern over their applicability of their population [68–70,72–77,79,81,84–87]. We deemed the populations of these studies to be not representative of the typical population. We found only one study [87] that excluded indeterminate index test results from diagnostic accuracy measures, to have an index test with high concern over applicability. For this reason, this study was excluded from meta-analysis. Five studies had a lack of information on the reference standard and so were classified as high concern over applicability [69,71,78,85,87].

Diagnostic accuracy of biomarker combination tests

Eighteen studies [68–70,72–84,86,87] evaluated 15 different biomarker combinations for detection of bacterial aetiology (Figs. 4

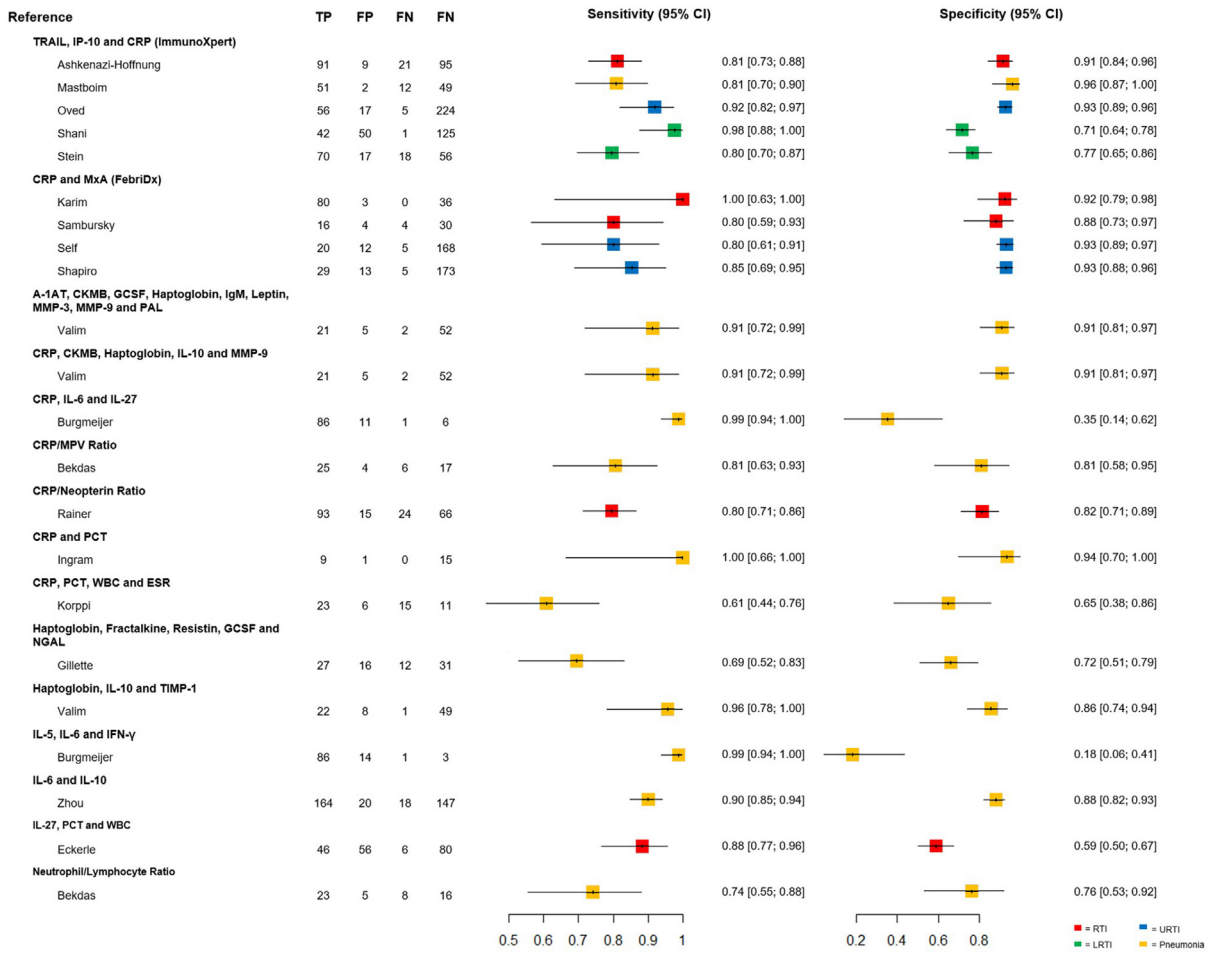

Fig. 4. Diagnostic performance of index tests to identify bacterial aetiology. Abbreviations: A-1AT, α-1 antitrypsin; CKMB, creatinine kinase myocardial band; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FN, false negatives; FP, false positives; GCSF, granulocyte colony-stimulating factor; IFN-γ, interferon-γ; IL-18, interleukin-18; IP-10, interferon-γ-induced protein 10; LRTI, lower respiratory tract infection; MMP-9, matrix metalloproteinase-9; MPV, mean platelet volume; MxA, myxovirus resistance protein 1; NGAL, neutrophil gelatinase-associated lipocalin; NPV, negative predictive value; PAL, phenylalanine ammonia-lyase-1; PCT, procalcitonin; RTI, respiratory tract infection; TBG, thyroxine-binding globulin; TIMP-1, tissue inhibitor of metalloproteinase-1; TN, true negatives; TP, true positives; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; URTI, upper respiratory tract infection; WBC, white blood cell count.

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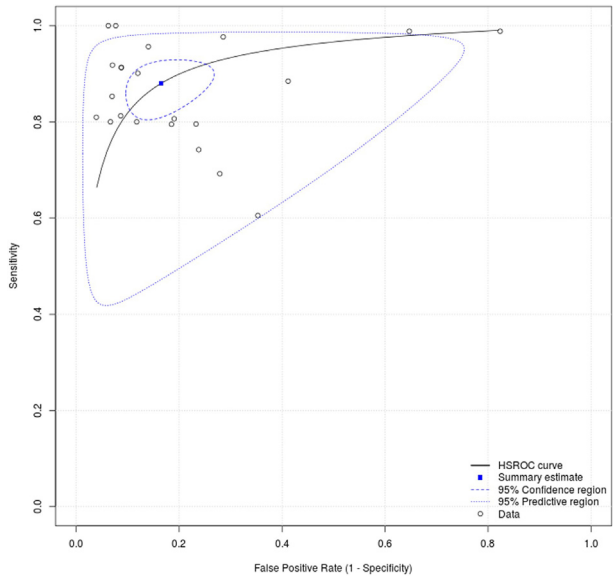

Fig. 5. Receiver operating characteristics plot of the diagnostic accuracy of all index tests identifying bacterial aetiology.

and 5, see Supplementary material, Tables S6 and S7). Sensitivity of 100% was reported by two studies, one using CRP and PCT (95% CI 66%–100%) [79] and a second using FebriDx (95% CI 63%–100%) [80]. Furthermore, these two studies showed the lowest rates of inappropriate antibiotic withholding in our hypothetical primary and secondary care populations [79,80]. The combination of CRP, PCT, white blood cell count and erythrocyte sedimentation rate produced the lowest sensitivity for bacterial infection with 61% (95% CI 44%–76%) [70]. We found the highest specificity to be 96% (95% CI 87%–100%) for the ImmunoXpert signature [86] and the lowest was 18% (95% CI 6%–41%) reported in a test consisting of interleukin-5, interleukin-6 and interferon-γ [75]. In our hypothetical populations, this ImmunoXpert study produced the lowest rates of inappropriately prescribed antibiotics [86].

There were 12 studies [68,69,71–73,78,80,82,83,85–87] using nine different biomarker combinations, detecting viral aetiology (Figs. 6 and 7, see Supplementary material, Tables S6 and S8). Sensitivity ranged from 97% (95% CI 85%–100%), reported for the FebriDx signature [80], to 59% (95% CI 50%–67%), reported for a combination of interleukin-27, PCT and white blood cell count [69]. This FebriDx study also showed the lowest rate of inappropriate viral management in our hypothetical populations [80]. Furthermore, the highest specificity for viral aetiology was 100% (95% CI 74%–100%) and the lowest percentages of patients inappropriately not treated for viral infection in our hypothetical populations was reported using FebriDx [80]. Lowest specificity was reported for a test consisting of a neutrophil: lymphocyte ratio with 74% (95% CI 74%–88%) [68].

ImmunoXpert

ImmunoXpert showed a pooled sensitivity of 85% (95% CI 75%–91%) and specificity of 86% (95% CI 73%–93%) for bacterial aetiology in 709 participants in four studies (Fig. 8) [78,81,84,86]. The two studies reporting diagnostic accuracy on lower RTIs showed lower specificity for bacterial aetiology [78,84]. When testing for viral aetiology, in 989 participants from three studies [71,78,86], an overall estimate for sensitivity was 90% (95% CI 79%–96%) and for specificity 92% (95% CI 83.0%–96%). Greater sensitivity for viral aetiology was shown in a generalized RTI population [71] and lower specificity was shown in a lower RTI population [78].

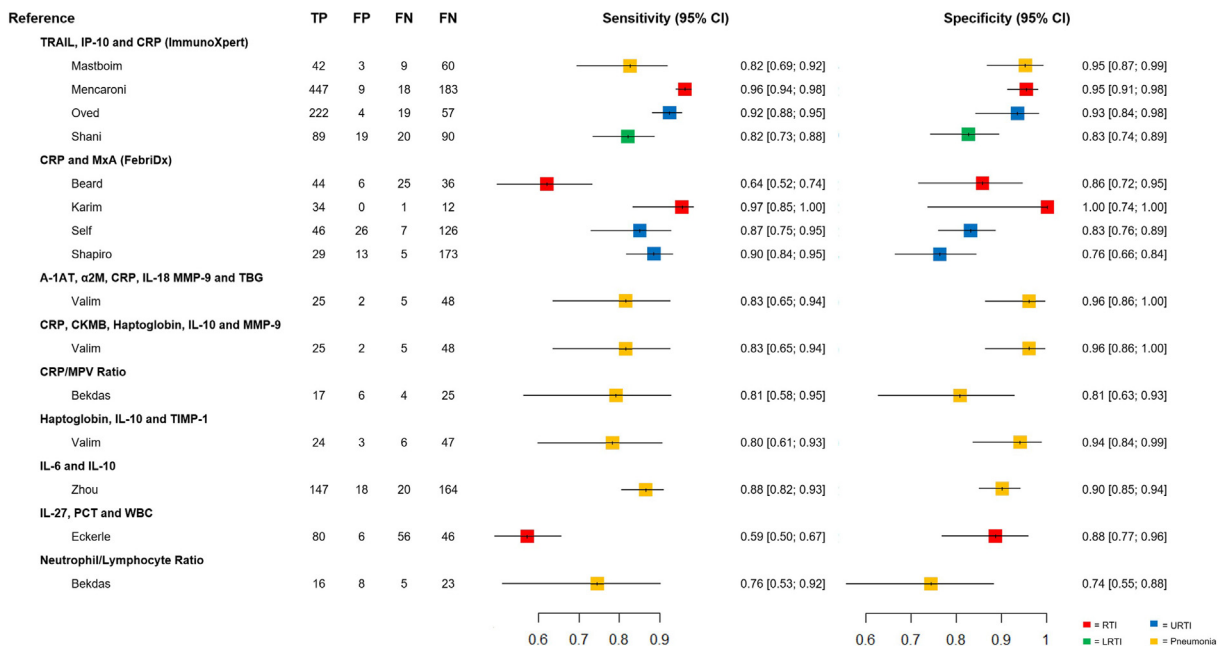

Fig. 6. Diagnostic performance of index tests to identify bacterial aetiology. Abbreviations: A-1AT, α-1 antitrypsin; α2m, α-2-macroglobulin; CKMB, creatinine kinase myocardial band; CRP, C-reactive protein; FN, false negatives; FP, false positives; IL-18, interleukin-18; IP-10, interferon-γ-induced protein 10; LRTI, lower respiratory tract infection; MMP-9, matrix metalloproteinase-9; MPV, mean platelet volume; MxA, myxovirus resistance protein 1; NPV, negative predictive value; PCT, procalcitonin; RTI, respiratory tract infection; TBG, thyroxine-binding globulin; TIMP-1, tissue inhibitor of metalloproteinase-1; TN, true negatives; TP, true positives; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; URTI, upper respiratory tract infection; WBC, white blood cell count.

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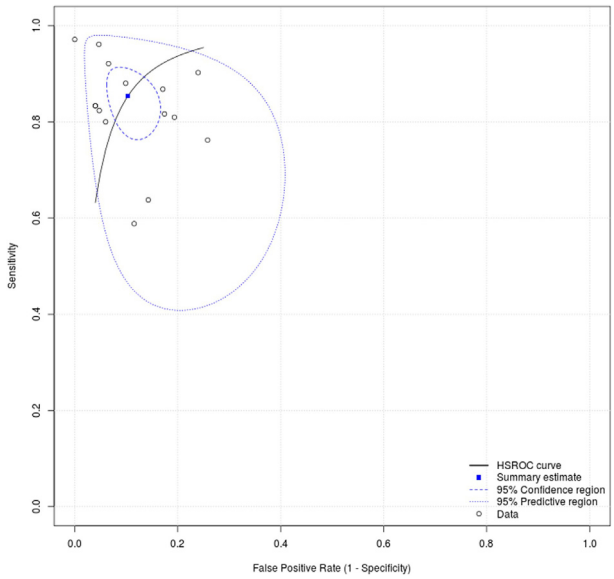

Fig. 7. Receiver operating characteristics plot of the diagnostic accuracy of all index tests identifying viral aetiology.

FebriDx

The FebriDx tool was tested for bacterial aetiology in 598 participants from four studies [77,80,82,83] with a pooled sensitivity of 84% (95% CI 75%–90%) and specificity of 93% (95% CI 90%–95%) (Fig. 9). When testing for viral aetiology, a sensitivity of 87% (95% CI 72%–95%) and a specificity of 82% (95% CI 66%–86%) was calculated from 583 participants from four studies [80,82,83,85]. Sensitivity and specificity did not significantly vary when testing in upper RTI compared to general RTI populations.

Positive and negative predictive values in hypothetical populations

The summative estimates for ImmunoXpert and FebriDx were compared with single biomarkers of CRP (cut-off 72 mg/mL: sensitivity 75.0%; specificity 82.0%) and PCT (cut-off 0.2 ng/mL: sensitivity 80.0%; specificity 86.0%) (Table 2) [88,89]. In both primary and secondary care, FebriDx-guided antibiotic prescription would result in the lowest rate of inappropriate prescription with comparable rates of inappropriate withholding.

Discussion

This systematic review demonstrates the potential clinical utility of a wide range of biomarker combination tests to distinguish acute bacterial and viral RTI aetiology. Summative estimates of two biomarker combinations, ImmunoXpert and FebriDx, outperformed the widely used single biomarkers of bacterial aetiology, CRP and PCT [88,89].

Currently, ImmunoXpert is only feasible in inpatient settings. Although an iteration with a 25-minute turnaround time is in development, this is still ill-suited for outpatient settings. In secondary care it is theorized to reduce antibiotic use by 78%–83% in two conference abstracts [78,86]. In hypothetical primary and secondary care populations, ImmunoXpert-guided antibiotic prescription resulted in less inappropriate prescriptions than that of CRP with lower rates of inappropriate withholding than CRP and PCT. Reducing inappropriate antibiotic use is important, not only for efficiency of treatment, but also for preventing the build up of antibiotic resistance in the community while maintaining low rates of inappropriate withholding is important in sustaining patient safety. ImmunoXpert has greater specificity for bacterial infections than CRP and outperformed single parameters of temperature, white blood cell count, CRP, PCT and absolute neutrophil count as well as radiological determination when tested in the same population [84,87,88]. However, the evidence base was judged to have a high overall risk for bias and estimated accuracy measures are imprecise with wide confidence intervals. Furthermore, a study by Oved et al. was excluded from meta-analysis [87] because participants with indeterminate index test results were excluded from analysis, which has been shown to artificially inflate test accuracy by up to 20% in similar populations [90,91]. Therefore, after contacting the authors without response, we felt this study could not be included in our meta-analysis.

FebriDx shows potential clinical utility in both primary and secondary care settings, with a turnaround time sufficient to be considered point-of-care in either, and specificity that is superior to CRP, PCT and ImmunoXpert for bacterial infection [88]. High specificity is advantageous in outpatient settings where infections tend to be less severe and reducing antibiotic prescription should be prioritized. In a small retrospective study in UK primary care, antibiotic prescriptions were reduced by 80% with no adverse effects when guided by FebriDx [92]. In our hypothetical inpatient

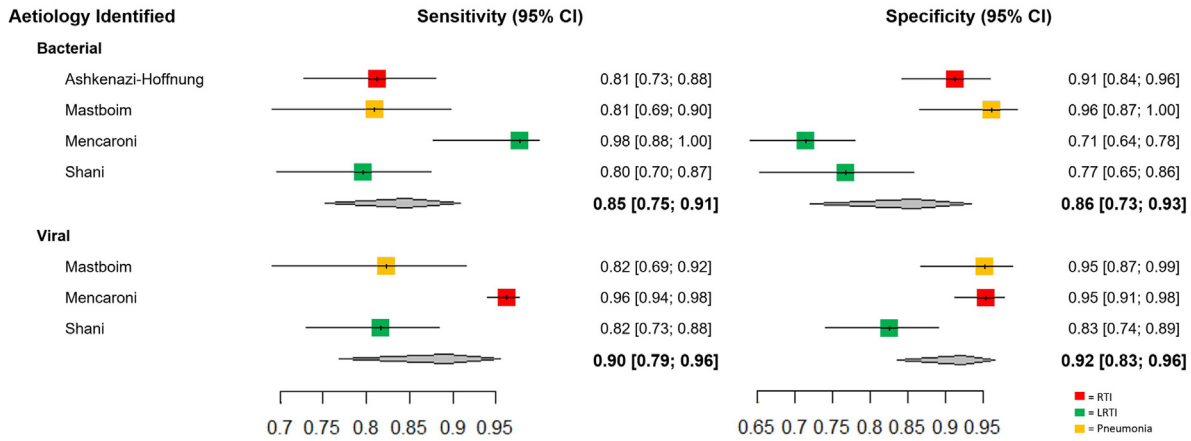

Fig. 8. Summative diagnostic performance of ImmunoXpert for bacterial and viral aetiology. RTI, respiratory tract infection; LRTI, lower RTI.

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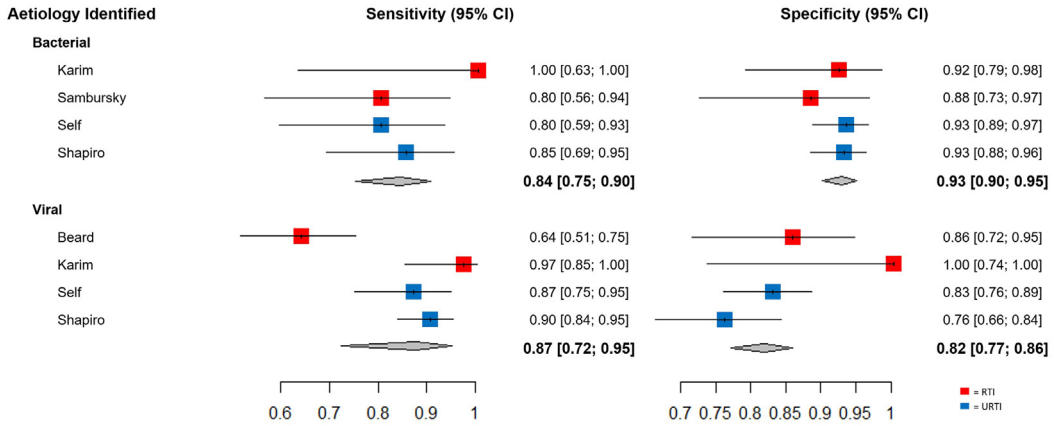

Fig. 9. Summative diagnostic performance of FebriDx for bacterial and viral aetiology. RTI, respiratory tract infection; URTI, upper RTI.

Table 2
Comparison of biomarker-guided antibiotic prescription in hypothetical primary and secondary care

Care environment	Biomarker test	Percentage of hypothetical population inappropriately prescribed antibiotics (95% CI)	Percentage of hypothetical population inappropriately withheld antibiotics (95% CI)
Primary care (bacterial aetiology prevalence 21%) [86]	CRP (cut-off 72 mg/mL) [88]	14.2	5.2
	PCT (cut-off 0.2 ng/mL) [89]	11.1	4.2
	ImmunoXpert	11.1 (5.5–21.3)	3.2 (1.9–5.2)
	FebriDX	5.5 (4.0–7.9)	3.4 (2.1–5.2)
Secondary care (bacterial aetiology prevalence 24%) [87]	CRP (cut-off 72mg/mL) [88]	13.7	6.0
	PCT (cut-off 0.2ng/mL) [89]	10.6	4.8
	ImmunoXpert	10.7 (5.3–20.5)	3.6 (2.2–6.0)
	FebriDX	5.3 (3.8–7.6)	3.8 (2.4–6.0)

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin.

and outpatient populations, FebriDx outperformed CRP, PCT and ImmunoXpert with the lowest rate in appropriate antibiotic use and comparable antibiotic withholding to ImmunoXpert. Although the evidence base is small, with only five studies identified, research was found to be of higher quality. Four studies were peer-reviewed articles and three were judged at low risk of bias.

The remaining biomarker combinations had unspecified turn-around times. Without means of rapid assessment, these combinations are incompatible with outpatient point-of-care testing. Standard hospital testing would return results in a feasible time for inpatients. Effective inpatient point-of-care testing requires high sensitivity for bacterial aetiology or high specificity for viral aetiology as infections tend to be more severe. However, these combinations showed mostly comparable or inferior diagnostic performance to standalone biomarkers, diminishing their potential clinical utility.

To the best of our knowledge, this is the first review focusing on the diagnostic accuracy of biomarker combinations identifying bacterial or viral acute RTI aetiology. A review by Thomas et al. [66] was restricted to a paediatric population with pneumonia and included index tests of biomarkers in isolation. As a result of differing inclusion criteria, we felt that our review focused on a gap in the current literature. Although we validated the use of the search filter, the possibility that a relevant publication was missed is a limitation. Additionally, our review excluded clinical prediction rules that combined biomarkers and clinical signs. Clinical features, particularly pyrexia [83], have a significant impact on pre-test probability as clinician assessment will influence decision-making alongside their understanding of a test result. All included studies had inclusion criteria specifying pyrexia and a further review would be warranted to explore the diagnostic accuracy of clinical features combined with biomarkers.

Limitations in the evidence base precluded robust interpretation and conclusions. The sparsity of data meant that summary estimates were relatively imprecise. Varying populations, target conditions, reference standards and study designs likely contributed to wide confidence intervals. The use of clinically relevant predictive values was limited by varying, and often high, prevalence of infection aetiologies in the study populations. We attempted to remedy this by using hypothetical populations with defined prevalence, but findings should be confirmed, particularly in outpatient studies. The validity and applicability of included studies was also a limitation with an overall high risk of bias observed in 18 studies and 16 studies having high population applicability concern. Case–control and nested case–control study designs have limited implications for clinical practice. Reducing the study population to clearly defined viral or bacterial infections makes it impossible to determine if tests are still accurate in a realistic population of possible viral, bacterial, fungal and parasitic infection, or other non-infectious cause. However, in a nested case–control study, cases and controls are selected from the same underlying cohort, which makes it less biased than a case–control study where cases and controls are recruited separately. Furthermore, the absence of a reference standard dictated a reliance on imperfect references. To be useful, such tests need to demonstrate a difference in outcomes, rather than just accuracy compared with a potentially inaccurate diagnostic standard. As a result of the numerous limitations in the evidence base we exercised caution in interpreting results and making recommendations.

Future research should aim to expand the current evidence base. Included studies were almost exclusively conducted in secondary care environments, limiting applicability to outpatients where point-of-care testing is arguably most required. Moreover, all studies included in this review were observational. This meant key

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secondary outcomes, that affect the adoption of testing, such as antibiotic reduction, adverse effects and cost-effectiveness analysis were limited. Future research should be experimental, in the form of randomized controlled trials, and aim to collect this information. This review is also not exhaustive of all possible candidate biomarkers that exhibit discriminatory ability. Expansion of the evidence bank will aid the discovery and evaluation of optimum combinations of biomarkers to determine acute RTI aetiology. Ultimately, no testing approach will be a panacea and future work must identify the optimal clinical context for each approach, factoring in cost, patient outcomes and antibiotic stewardship.

Conclusion

A wide variety of biomarker combinations show potential clinical utility. However, current research is overshadowed with bias and is insufficient to make recommendations, especially in primary care where the evidence is entirely lacking. The FebriDx and ImmunoXpert detection tools show significant potential to discriminate aetiology and reduce unnecessary antibiotic prescription. Future research should aim to grow the evidence base in primary care and experimentally evaluate patient outcomes and cost-effectiveness.

Transparency declaration

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Author contributions

Conception was by ME and JS; search strategy was by SD and design was by ME, JS and HC. Data collection and analysis were by HC and ME. All the authors interpreted the findings and clinical expertise was PM. First draft of the manuscript was produced by HC; all authors contributed to drafting and critical revisions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.05.018.

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